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June 20, 2005 Michael C. Barrett
Date

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Mumper *et al.*

Serial No.: 10/072,320

Filed: February 7, 2002

For: pH-Sensitive Mucoadhesive Film-Forming Gels and Wax-Film Composites Suitable for Topical and Mucosal Delivery of Molecules

Group Art Unit: 1615

Examiner: Retford O. Berko

Atty. Dkt. No.: NANO:002USD1/MCB

APPEAL BRIEF

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APPEAL BRIEF

BOX AF
Commissioner of Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant submits an original and three copies of this Appeal Brief to the Board of Patent Appeals and Interferences in response to the final Office Action dated November 17, 2004 and the Advisory Actions dated February 8, 2005, and April 4, 2005. The Notice of Appeal was received by the Patent Office on March 18, 2005, as indicated by a stamped postcard. A one-month extension and associated fee is concurrently filed with this Appeal Brief to bring the due date to June 20, 2005 (June 18th falls on a Saturday). The $250.00 filing fee for this Appeal Brief is included.

Applicant believes that no additional fees are due; however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is authorized to deduct those fees from Fulbright & Jaworski Deposit Account No. 50-1212/NANO:002USD1/MCB. If overpayment is included, the Commissioner is authorized to credit that account.

Please date stamp and return the attached postcard as evidence of receipt.

I. REAL PARTY IN INTEREST

The real party in interest is the assignee, University of Kentucky Research Foundation.

II. RELATED APPEALS AND INTERFERENCES

The present case is a divisional patent application. Its parent application is U.S. Serial No. 09/748,133, which is currently under appeal. A supplemental appeal brief was filed in the parent case on March 30, 2004. Applicant has not received an Answer. Applicant inquired about the status of the appeal at or around December 7, 2004. The Examiner was unable to provide a timetable regarding an Answer.

III. STATUS OF CLAIMS

Claims 1–62 were originally filed on December 27, 2000 in parent application, Serial No. 09/748,133. On February 2, 2002, the present divisional application was filed. Upon filing, claims 1-32 and 59-62 were canceled, leaving claims 33-58 pending. In response to an oral species election requirement on January 5, 2004, Applicant elected without traverse the alleged species of claim 51 and allowed claims 48-50 and 52-55 to be withdrawn.[1] As of January 5, 2005, claims 33-47, 51, and 56-58 were therefore pending. In response to the first Office Action dated February 2, 2004, claims 35-41, 44, 46-47, 51, and 56-57 were amended.[2] In response to a

[1] The Office Action mailed February 2, 2004 mistakenly lists the claims associated with the species election.

[2] The Amendment and Response to the Office Action Dated February 2, 2004, which was mailed on April 27, 2004, mistakenly lists the pending claims.

Final Office Action dated November 17, 2004, claims 33 and 35 were amended, and claim 58 was canceled. However, in Advisory Actions dated February 8, 2005, and April 4, 2005, the entry of those amendments was refused.[3] Claims 33-47, 51, and 56-58 are therefore currently pending. Claim 33 is the only independent claim. Each pending claim is rejected and is being appealed here.

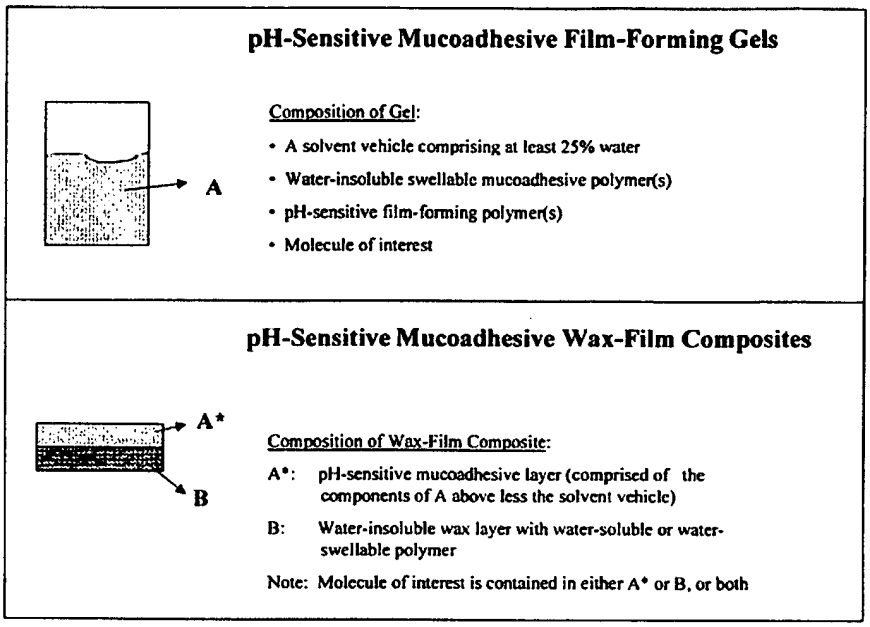
IV. STATUS OF AMENDMENTS

On January 18, 2005, claim amendments were filed in response to the Final Office Action dated November 17, 2004. Claims 33 and 35 were amended, and claim 58 was canceled. In Advisory Actions dated February 8, 2005, and April 4, 2005, the entry of those amendments was refused. No amendments are being filed with this Appeal Brief.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The invention generally concerns a particular "wax-film composite," which is defined as a bi-layer film with bonded layers. *See* specification, page 18, 2nd full paragraph. The bi-layer composite includes (1) a pH-sensitive mucoadhesive layer bonded to (2) a water-insoluble wax layer. *See id.* The bottom half of Figure 1 illustrates a representative, but non-limiting embodiment as follows:

[3] Applicant respectfully submits that it was improper for the Office to refuse entry of such amendments, does not acquiesce in the Office's justification for refusing entry, and reserves the right to traverse the Office's justification, if necessary.



The pH-sensitive mucoadhesive layer may be present at a concentration of 20% to 90% by weight, and the water-insoluble wax layer may be present at a concentration of 10% to 80% by weight. *See* specification, page 7, 1st paragraph and page 18, 2nd full paragraph. The pH-sensitive mucoadhesive layer may include (1) at least one water-insoluble swellable mucoadhesive polymer, (2) at least one pH-sensitive film-forming polymer, and (3) at least one molecule of interest. *See* specification, page 7, 1st paragraph; *see also* Figure 1. The water-insoluble swellable mucoadhesive polymer may be polyacrylic acid cross-linked with polyalkenyl ether or divinyl glycol. *See* specification, page 7, 2nd paragraph. The water-insoluble swellable mucoadhesive polymer may be Noveon or Carbomer. *See id.* The water-insoluble swellable mucoadhesive polymer may be present in the pH-sensitive mucoadhesive layer at a concentration from 0.1% to 20% by weight. *See id.* The pH-sensitive film-forming polymer present in the pH-sensitive mucoadhesive layer may be a copolymer of methacrylic acid and acrylic or methacrylic ester. *See* specification, page 7, 3rd paragraph. The pH-sensitive film-forming polymer may be present in the pH-sensitive mucoadhesive layer at a concentration from 0.05% to 10% by weight. *See* specification, page 7, 5th paragraph. The pH-sensitive film-

forming polymer present in the pH-sensitive mucoadhesive layer may be a Eudragit polymer, or chemical derivative thereof. *See* specification, page 7, 3rd paragraph.

The water-insoluble wax layer may include at least one water-insoluble pharmaceutical wax having a melting point between 40° C and 100° C and at least one water-soluble or water-swellable polymer. *See* specification page 7, 4th paragraph and page 18, 1st full paragraph. The wax may be DENTSPLY® Utility Wax, beeswax, emulsifying wax, microcrystalline wax, carnauba wax, paraffin wax, white wax, yellow wax, or other suitable pharmaceutical wax. *See* specification, page 7, 5th paragraph. The water-soluble or swellable polymer may be present in the insoluble wax layer at a concentration from 0.05% to 10% by weight. *See id.* The water-soluble or water-swellable polymer may be tragacanth, polyvinyl, pyrrolidone, polyvinyl alcohol, cross-linked polyacrylic acid, polyethylene glycol, a cellulose polymer derivative, or other suitable pharmaceutical polymer that is water-soluble or water-swellable. *See* specification, paragraph spanning pages 7-8.

The molecule of interest may be contained in and released from either the pH-sensitive mucoadhesive layer or the water-insoluble wax layer. *See* Specification, page 8, 1st incomplete paragraph; *see also* Figure 1. The molecule of interest may include an active pharmaceutical compound such as an antimicrobial, antiviral, antiinflammatory, antiseptic, antihistimine, a local anesthetic, a disinfectant, a keratolytic, an analgesic, an anti-migrane, anti-fungal, a sweetner, a flavoring agent, a diagnostic agent, or a combination thereof. *See* specification, page 8, 1st full paragraph. The molecule of interest may be a peptide or protein. *See id.*

The wax-film composite may be applied to an application site including: the skin, mouth, vagina, nasal cavity, or other accessible mucosal site. *See* specification, page 8, 1st full

paragraph. The wax-film composite may adhere to the application site for at least one hour. *See id.* The wax-film composite may have a total thickness of less than 5 mm. *See id.*

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following ground of rejection is presented for review: the rejection of each pending claim (claims 33-47, 51, and 56-58) under 35 U.S.C. § 103 for allegedly being obvious in view of U.S. Patent No. 4,959,218 ("Eckenhoff") combined with U.S. Patent No. 5,700,478 ("Biegajski").

VII. ARGUMENT

A. Substantial evidence is required to uphold the Examiner's position

Applicant notes that findings of fact and conclusions of law by the U.S. Patent and Trademark Office must be made in accordance with the Administrative Procedure Act, 5 U.S.C. § 706(A), (E), 1994. *Dickinson v. Zurko*, 527 U.S. 150, 158 (1999). Moreover, the Federal Circuit has held that findings of fact by the Board of Patent Appeals and Interferences must be supported by "substantial evidence" within the record. *In re Gartside*, 203 F.3d 1305, 1315 (Fed. Cir. 2000). In *Gartside*, the Federal Circuit stated that "the 'substantial evidence' standard asks whether a reasonable fact finder could have arrived at the agency's decision." *Id.* at 1312.

Accordingly, an Examiner's position on Appeal must be supported by "substantial evidence" within the record in order to be upheld by the Board of Patent Appeals and Interferences.

B. The cited references do not, and cannot, support a *prima facie* case of obviousness for claim 33

Independent claim 33 has been rejected as obvious based on the combination of Eckenhoff and Biegajski (collectively, the "cited references"). The Office has not established a *prima facie* case of obviousness, and this rejection should be withdrawn.

Three basic criteria must be met to establish a *prima facie* case of obviousness:

(1) the prior art reference (or references when combined) must teach or suggest all the claim limitations;

(2) there must be some suggestion or motivation, either in the References themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; and

(3) there must be a reasonable expectation of success.

See M.P.E.P. § 2142.

Here, the Office has not established a *prima facie* case because it has not established any of these three prongs. Even if the cited references were combined, the features of claim 33 would not be disclosed, taught, or suggested.

Independent claim 33 recites: "A wax-film composite comprised of a pH-sensitive mucoadhesive layer and a water-insoluble wax layer." Claim terms must be interpreted according to their definition in the specification. M.P.E.P. § 2111.01; *Liquid Dynamics Corp. v. Vaughan Co.*, 355 F.3d 1361, 1367 (Fed. Cir. 2004) ("The specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication") (citing *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). Here, the specification defines "wax-film composite" to mean a bi-layer, bonded film.[4] *See* specification, page 18, 2nd full paragraph ("A wax-film composite refers to a *bi-layer film* comprised of a pH-sensitive mocoadhesive layer and a water-insoluble wax layer. ... *For bonding the two layers* of the bi-layer wax-film composite, it is preferred that ... .") (emphasis added). The term "pH-sensitive" is defined as "a substance that is affected by changes in pH so that the substance changes conformation, charge, solubility, or combinations thereof." *See* specification, page 16

[4] Applicant notes that claim 33 encompasses structures having three or more film layers and/or other features, if such structures somewhere include the recited, bonded bi-layer film including (1) the pH-sensitive mocoadhesive layer and (2) the water-insoluble wax layer.

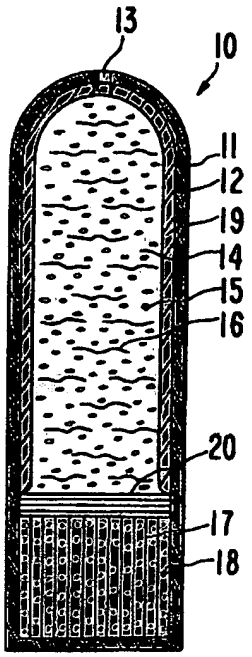
2nd full paragraph. "Mucoadhesive" is defined as "a substance that sticks to or adheres to the skin or mucosal surfaces by forces that are measurable and by any number of mechanisms such as, but not limited to the following: hydrogen-bonding, ionic interaction, hydrophobic interaction, van der Waals interaction, or combinations thereof." *See* specification, page 19, 1st full paragraph. As discussed below, the cited art, taken alone or in combination, does not teach or suggest the bonded, bi-layer film including (1) a pH-sensitive mucoadhesive layer and (2) a water-insoluble wax layer of claim 33 and as defined by the specification.

1. Eckenhoff and Biegajski, alone or in combination, do not disclose, teach, or suggest all the features of claim 33

a) Eckenhoff does not disclose, teach, or suggest key features of claim 33, leaving unmet claim elements

Eckenhoff is directed to a dispensing device that uses a driving member (*e.g.*, a swellable hydrophilic polymer) to push a beneficial agent (*e.g.*, a drug) through a wall, *via* an orifice, into an animal. *See* Eckenhoff, column 5, lines 1-58; column 10, line 31; column 11, lines 22-24; *see also* Figure 3. The structure and function of the Eckenhoff device (and, the significant differences with the present invention) may be readily seen with reference to Figure 3:

FIG.3



Wall **12** (dark blue) encloses lumen **14** (yellow). Eckenhoff, column 5, lines 5-7. Within lumen **14** (yellow) is a first composition **15**, such as a drug, represented by dots. Eckenhoff, column 5, lines 20-23; column 10, lines 28-32. Means **19** (red), which may be a coating, protects the drug from fluid. Eckenhoff, column 5, lines 36-38, 47-50. In operation, driving member **17** (green) swells to physically push the drug from lumen **14** (yellow) through means **19** (red) and wall **12** (dark blue), *via* passageway **13** (pink). Eckenhoff, Abstract; column 1, lines 14-25; column 3, lines 28-34; column 5, lines 1-58 (describing individual illustrated components); column 6, lines 29-34 (describing operation). In this manner, a drug can literally be "squeezed-out" of this device and delivered into an animal. Layer **20** (light blue) prevents fluid associated with driving member **17** (green) from passing into lumen **14** (yellow) and also ensures that the driving forces from the driving member **17** (green) are applied directly against the drug within lumen **14** (yellow). Eckenhoff, column 6, lines 20-29. Conceptually, the device of Eckenhoff

can accordingly be compared, at a high level, to a tube of toothpaste, which works by the toothpaste tube being squeezed to release toothpaste out of the top of the tube.

The subject matter of claim 33 is clearly and substantially different than the subject matter of Eckenhoff. Eckenhoff does not disclose, teach or suggest any mucoadhesive layer, much less the pH-sensitive mucoadhesive layer of claim 33. Instead of sticking or adhering to the skin or mucosal surfaces, the Eckenhoff device is implanted, using implanting or injecting instruments, by pushing the device into an implantation receiving site:

> **Another object of the invention is to provide a drug delivery device that is implantable, is compact in size and shape to allow easy placement within the lumen of trocars and similar implanting or injecting instruments that are limited dimensions and, consequently, are essentially free of undue trauma and discomfort to a receiving animal.**
>
> **Another object of the invention is to provide a delivery device shaped at the ends in a conical or spherical shape for reducing the force necessary to push the device into the implantation receiving site, thereby reducing the incidence of tissue damage and the incidence of damage to the delivery device, and enhancing the process of implantation**

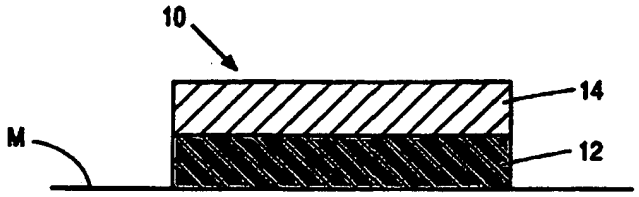
Eckenhoff, column 3, lines 49-62 (emphasis added); also column 7, lines 15-16 (discussing the ease of implantation in a subcutaneous space). Because implantation is the mechanism used in Eckenhoff, a mucoadhesive layer is nowhere even contemplated, nor is there any motivation (or need) for such a layer. In fact, Eckenhoff teaches away from a mucoadhesive layer because instead, and in contrast, an explicit "object" of the Eckenhoff invention is to provide an implantable device that is pushed into the receiving site with injecting instruments.

Because a pH-sensitive mucoadhesive layer is totally absent, Eckenhoff necessarily fails to disclose, teach, or suggest the associated wax-film composite of claim 33, which includes such pH-sensitive mucoadhesive layer. Moreover, although Eckenhoff mentions that layer **20** (light blue, above) may be wax and may be used to separate the driving member **17** (green, above) from the lumen **14** (yellow, above), that wax layer is not bonded to or associated with any pH-

sensitive mucoadhesive layer, as in claim 33. In sum, Eckenhoff lacks a disclosure, teaching, and suggestion for at least claim 33's pH-sensitive mucoadhesive layer and wax-film composite. The other cited art, Biegajski, does not cure these deficiencies.

b) Biegajski does not disclose, teach, or suggest key features of claim 33, leaving unmet claim elements

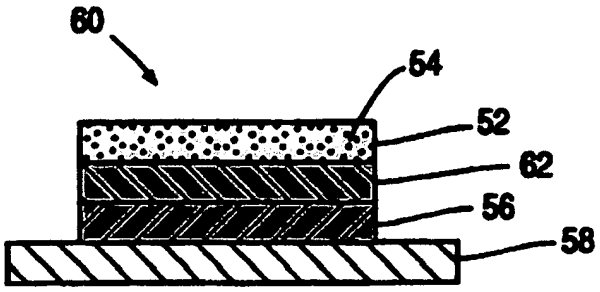
Biegajski is directed to water soluble pressure-sensitive adhesives that include a water-soluble polymer that is made tacky at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer. Biegajski, Abstract. Figure 1 of Biegajski illustrates a representative bilaminate:



Here, the basal adhesive layer **12** (blue) adheres to mucosal surface **M**, and upper polymer layer **14** (yellow) and/or basal adhesive layer **12** (blue) may deliver substances. Biegajski, column 16, lines 1-24. Upper polymer layer **14** (yellow) dissolves first and its dissolution is substantially complete when dissolution of the basal adhesive layer **12** (blue) begins. *Id.* Biegajski repeatedly explains that each layer is water soluble so that the device can eventually fully dissolve within a body cavity in which it is placed. *See, e.g.*, Biegajski, column 3, lines 35-41, column 4, lines 57-63; column 5, lines 11-15; and column 9, lines 18-22.

In some "trilaminate" embodiments of Biegajski, a third water-soluble layer called an occluding layer is placed between, *e.g.*, the blue and yellow layers shown above. Biegajski explains that this may be useful in situations in which one wants to limit a particular substance in an upper layer from bleeding into the lower layer before the upper layer is completely

dissolved—this can be accomplished if the occluding layer is substantially impermeable to the particular substance found in the uppermost layer. *See* Biegajski, column 4, lines 21-46; *see also* column 5, lines 41-54. One disclosed occluding layer is a water-soluble polymer composition with a wax "additive." Biegajski, column 4, lines 35-39. Another disclosed occluding layer includes a Eudragit family of polymethacrylic copolymers. Biegajski, column 22, lines 4-22. Figure 9 of Biegajski illustrates a representative trilaminate:



This figure shows polymer layer **52** (yellow), which contains an active substance, adhesive layer **56** (blue), and the additional polymer layer **62** (green) for occlusion (uncolored structure **58** is simply a release liner). *See* Biegajski, column 22, lines 23-32; column 4, lines 35-39 (calling the third layer an occluding layer). The use of the third layer (green), as well as other layers throughout Biegajski allows one to effectively control release rates. *See* Biegajski, column 4, lines 8-20, 35-46; and column 9, liens 29-32.

The subject matter of claim 33 is clearly and substantially different than the subject matter of Biegajski. First, Biegajski does not disclose, teach or suggest the pH-sensitive mucoadhesive layer of claim 33. Particularly, the adhesive layers (*e.g.*, blue adhesive layer **56,** above) of Biegajski are not disclosed or suggested as constituting a substance that is affected by changes in pH so that the substance changes conformation, charge, solubility, or combinations thereof. Even if occluding layer **62** (green, above) of Biegajski includes a Eudragit, there is still no "pH-sensitive mucoadhesive layer" because Biegajski's adhesive layer **56** (blue) is not *itself*

pH-sensitive—rather, the distinct layer above it may be. Claim 33 recites that it is the mucoadhesive layer that is pH-sensitive, not a separate layer somewhere else in a structure.

Second, Biegajski does not disclose, teach, or suggest the "water-insoluble wax layer" of claim 33. Instead, as mentioned above, Biegajski stresses that layers should be *water-soluble* so that delivery devices may dissolve completely. *See, e.g.*, Biegajski, column 3, lines 35-41, column 4, lines 57-63; column 5, lines 11-15; and column 9, lines 18-22. Biegajski's disclosure of a wax "additive" in a third, water-soluble layer acting as an occluding layer (column 4, lines 35-39) does not amount to disclosure or even a suggestion of a non-soluble wax layer at least because a wax additive is not a layer, and a water-*soluble* layer does not suggest a water-*insoluble* layer.

Third, Biegajski does not disclose, teach, or suggest the "wax-film composite" because a pH-sensitive mucoadhesive layer and water-insoluble wax layer are totally absent.

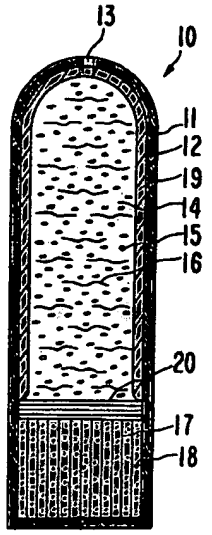
In sum, Biegajski lacks a disclosure, teaching, and suggestion for at least claim 33's pH-sensitive mucoadhesive layer, water-insoluble wax layer, and wax-film composite. Combining Eckenhoff with Biegajski does not cure these deficiencies.

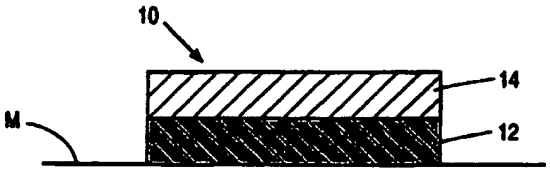
c) Eckenhoff combined with Biegajski do not disclose, teach, or suggest each feature of claim 33, leaving unmet claim elements

The significant deficiencies of Eckenhoff and Biegajski explained above are not remedied through their combination. The Office argues that claim 33 is met if the wax of Eckenhoff is combined with the bilaminate of Biegajski. *See* Final Office Action, pages 7-8. Respectfully, the Office's argument is incorrect. Ignoring for now the lack of any motivation to combine the disparate technologies of Eckenhoff and Biegajski (discussed below), somehow placing the light blue wax layer **20** of Eckenhoff (below, left) into the bilaminate of Biegajski

(below, right) yields a structure nothing like that recited in claim 33 and as defined by the specification:

FIG.3



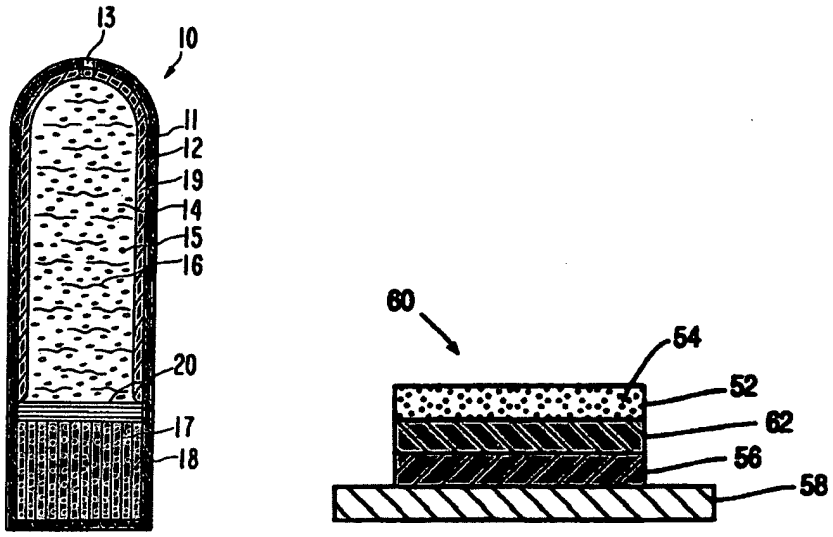


At best, what would be yielded through this combination would be a tri-layer structure including a non-pH-sensitive adhesive layer, an upper polymer layer, and a wax layer. Hence, this combination would still be lacking both the required pH-sensitive mucoadhesive layer (lacking in Biegajski as explained above) and the wax-film composite (due at least to the absence of the pH-sensitive mucoadhesive layer and the lack of an appropriate bonded bi-layer film).

If the combination contemplated by the Office is *replacing* the upper polymer layer (yellow, above right) with a wax layer (light blue, above left), the result is the same—there is no pH-sensitive mucoadhesive layer (lacking in Biegajski as explained above) and hence, no wax-film composite.

If the Office contemplates combining the device of Eckenhoff (below, left) with a trilaminate of Biegajski (below, right), the elements of claim 33 are still not met:

FIG.3



Placing the light blue wax layer **20** of Eckenhoff somewhere in the trilaminate of Biegajski cannot cure Biegajski's lack of a pH-sensitive mucoadhesive layer and hence cannot cure the lack of even a suggestion of a wax-film composite. Likewise, replacement of one or more of Biegajski's trilaminate layers with a wax layer does not convert anything into a pH-sensitive mucoadhesive layer, much less a bonded bi-layer film having the requisite components set forth in claim 33.

Because the cited references fail to teach or suggest all the claim limitations of claim 33, even when the cited references are combined, the first prong of obviousness is not met, and Applicant therefore respectfully requests that the present obviousness rejection be withdrawn.

2. There is no suggestion or motivation to combine Eckenhoff and Biegajski

There is no motivation or suggestion in the cited references for combining Eckenhoff and Biegajski. Eckenhoff is directed to a specialized implantable device that is pushed into a receiving site with injecting instruments, and there is therefore no motivation for any combination with the laminate structures of Biegajski, which adhere to surfaces.

Additionally, Biegajski stresses that its layers are water-soluble for full dissolution. *See, e.g.*, Biegajski, column 3, lines 35-41, column 4, lines 57-63; column 5, lines 11-15; and column

9, lines 18-22. Biegajski therefore teaches away from incorporation of any water-insoluble wax layer, which exemplifies why the combination of the cited references cannot stand under the law. *Tec Air, Inc. v. Denso Mfg. Michigan Inc.*, 192 F.3d 1353, 1359-1360 (Fed. Cir. 1999) ("There is no suggestion to combine, however, if a reference teaches away from its combination with another source.").

There is also no motivation for ruining or jeopardizing Biegajski's important water-solubility feature through combination with Eckenhoff's wax layer because to do so would fundamentally change the operation of Biegajski—instead of having a fully-dissolvable device that can controllably release a substance, one would be left with a device that does not dissolve fully and that would include a layer that would arguably prevent one or more other layers from the opportunity to effectively deliver any substance. This too exemplifies why there is legally no motivation to combine. *Tec Air,* 192 F.3d at 1360 ("If when combined, the references 'would produce a seemingly inoperative device,' then they teach away from their combination.") (citing *In re Sponnoble*, 405 F.2d 578, 587 (CCPA 1969)); *see also In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984) (finding no suggestion to modify a prior art device where the modification would render the device inoperable for its intended purpose).

Any combination of bi- or trilaminates or other features from Biegajski into Eckenhoff would also be improper. Eckenhoff essentially delivers a substance to an individual by implanting a device using injecting instruments and squeezing a substance out of a lumen of the device (by expanding a swellable polymer) so that the substance flows through an orifice, as explained above. There is nothing within Eckenhoff or Biegajski to suggest incorporation of bi- or trilaminates into such a specialized device with a specialized manner of operation.

Applicant respectfully notes that the Office's attempt to combine Eckenhoff with Biegajski runs afoul of fundamental tenets of patent law. Proposed modifications to the cited art cannot render that art unsatisfactory for its intended purpose, and the modification cannot change the principle of operation of a reference. M.P.E.P. § 2143.01. Even if aspects of Eckenhoff with Biegajski may be physically combinable, "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." M.P.E.P. § 2143.01 (*citing In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)). Further, where the teachings of the prior art conflict as they do here with respect to solubility of layers and manners of operation, "the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another," which has not been done. M.P.E.P. § 2143.01 (*citing In re Young*, 18 USPQ2d 1089 (Fed. Cir. 1991)). To combine the references despite any motivation, as has been done here, amounts to impermissible hindsight. *See Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5 (Fed. Cir. 1986) (noting that references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention).

Because there is no motivation to combine the cited references, Applicant respectfully requests that the present obviousness rejection be withdrawn.

3. There is no reasonable expectation of success associated with the combination of Eckenhoff and Biegajski

There is nothing in the cited references that demonstrates a reasonable expectation of success surrounding the combination of Eckenhoff and Biegajski. The Office's analysis of this factor is conclusory and, respectfully, not fully understood by Applicant. *See* Final Office Action, page 8. The reasonable expectation of success for establishing obviousness "must be

founded in the prior art, not in the applicant's disclosure." *Noelle v. Lederman*, 355 F.3d 1343, 1352 (Fed. Cir. 2004); *also In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Here, nothing within Eckenhoff or Biegajski establish a reasonable expectation of success concerning the significant modifications of the references proposed by the Office. As discussed above, modifying the references as suggested by the Office is taught away, and if implemented, would yield devices that do not operate at all, or at least not for their intended purpose.

Because none of the three prongs of obviousness have been established, there is no *prima facie* case of obviousness, and Applicant correspondingly requests removal of the current rejection to claim 33.

C. The cited references do not, and cannot, support a *prima facie* case of obviousness for dependent claims 34-47, 51, or 56-58, considering each claim independently from the other

Claims 34-47, 51, and 56-58 are rejected in view of the same combination cited in the rejection of claim 33. *See* Office Action, pages 4-8. Each of these claims is patentable for independent reasons. Dependent claims 34-47, 51, and 56-58 include several requirements above and beyond independent claim 33. It appears that the Office has focused its attention on independent claim 33, and it has correspondingly provided few clues as to why particular aspects of these dependent claims are believed to be unpatentable. No *prima facie* case of obviousness has been established with respect to any of the dependent claims, and Applicant respectfully requests that the rejections be withdrawn.

For instance, claim 34 requires (in addition to the elements of claim 1):

- the solvent vehicle is comprised of at least 25 to 100 parts water or buffered water with 0 to 75 parts of ethanol, propylene glycol, glycerin, polyethylene glycol, or combinations thereof

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 34 requires (in addition to the elements of claim 33):

- the pH-sensitive mucoadhesive layer is present at a concentration of 20% to 90% by weight, and the water-insoluble wax layer is present at a concentration of 10% to 80% by weight.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 35 requires (in addition to the elements of claim 33):

- the pH-sensitive mucoadhesive layer includes at least one water-insoluble swellable mucoadhesive polymer, at least one pH-sensitive film-forming polymer, and at least one molecule of interest.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established. For example, no layer in Biegajski or Eckenhoff includes such elements, and to pluck such elements from other unrelated portions in the references to arrive at the claimed composition would amount to impermissible hindsight reconstruction. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448 (Fed. Cir. 1986) ("It is impermissible within the framework of 35 U.S.C. § 103 to pick and choose from any on reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art."); *W.L. Gore Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983) ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, where no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.").

Claim 36 requires (in addition to the elements of claim 35):

- the water-insoluble swellable mucoadhesive polymer is polyacrylic acid cross-linked with polyalkenyl ether or divinyl glycol.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 37 requires (in addition to the elements of claim 35):

- the water-insoluble swellable mucoadhesive polymer is Noveon or Carbomer.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 38 requires (in addition to the elements of claim 35):

- the water-insoluble swellable mucoadhesive polymer is present in the pH-sensitive mucoadhesive layer at a concentration from 0.1% to 20% by weight.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 39 requires (in addition to the elements of claim 35):

- the pH-sensitive film-forming polymer present in the pH-sensitive mucoadhesive layer is a copolymer of methacrylic acid and acrylic or methacrylic ester.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 40 requires (in addition to the elements of claim 35):

- the pH-sensitive film-forming polymer is present in the pH-sensitive mucoadhesive layer at a concentration from 0.05% to 10% by weight.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 41 requires (in addition to the elements of claim 35):

- the pH-sensitive film-forming polymer present in the pH-sensitive mucoadhesive layer is a Eudragit polymer, or chemical derivative thereof.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 42 requires (in addition to the elements of claim 33):

- the water-insoluble wax layer comprises at least one water-insoluble pharmaceutical wax having a melting point between 40° C and 100° C and at least one water-soluble or water-swellable polymer.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 43 requires (in addition to the elements of claim 42):

- the wax is DENTSPLY® Utility Wax, beeswax, emulsifying wax, microcrystalline wax, carnauba wax, paraffin wax, white wax, yellow wax, or other suitable pharmaceutical wax.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 44 requires (in addition to the elements of claim 42):

- the water-soluble or swellable polymer is present in the insoluble wax layer at a concentration from 0.05% to 10% by weight.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 45 requires (in addition to the elements of claim 42):

- the water-soluble or swellable polymer is tragacanth, polyvinyl, pyrrolidone, polyvinyl alcohol, cross-linked polyacrylic acid, polyethylene glycol, a cellulose polymer derivative, or other suitable pharmaceutical polymer that is water-soluble or water-swellable.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 46 requires (in addition to the elements of claim 35):

- the molecule of interest is contained in and released from either the pH-sensitive mucoadhesive layer or the water-insoluble wax layer.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 47 requires (in addition to the elements of claim 35):

- the molecule of interest comprises an active pharmaceutical compound such as an antimicrobial, antiviral, antiinflammatory, antiseptic, antihistimine, a local anesthetic, a disinfectant, a keratolytic, an analgesic, an anti-migrane, anti-fungal, a sweetner, a flavoring agent, a diagnostic agent, or a combination thereof.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 51 requires (in addition to the elements of claim 35):

- the molecule of interest is a peptide or protein.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 56 requires (in addition to the elements of claim 33):

- the wax-film composite is applied to an application site comprising: the skin, mouth, vagina, nasal cavity, or other accessible mucosal site.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 57 requires (in addition to the elements of claim 56):

- the wax-film composite adheres to the application site for at least one hour.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 58 requires (in addition to the elements of claim 33):

- the wax-film composite has a total thickness of less than 5 mm.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established. The recited thickness requirement can affect, among other things, adhesion time and is advantageous in, *e.g.*, allowing the claimed composite to be adhered within a mouth almost unnoticed. The thickness requirement of the claimed wax-film composite is nowhere disclosed or suggested in the cited references. In

particular, the cited references do not envision the wax-film composite being claimed (as discussed extensively here), much less a wax-film composite that is a thin-film less than 5 mm as recited in claim 58. This additional and important distinction between the cited references and the invention further exemplifies that the present claims are patentable, despite the current rejections.

D. The Office's arguments and rebuttals to Applicant's arguments do not establish or bolster any *prima facie* case of obviousness

In the first and final Office Actions, the Office impermissibly uses hindsight reconstruction in an attempt to piece together Applicant's invention using Applicant's specification as a blueprint, in contradiction to tenets of patent law. *Bausch & Lomb*, 796 F.2d at 448; *W.L. Gore*, 721 F.2d at 1553; *Hodosh*, 786 F.2d at 1143 n.5. This can be seen, *e.g.*, at pages 4-6 of the Final Office Action, where disparate elements from separate portions of the cited references are argued to render Applicant's claims obvious.

As discussed above, the cited references differ significantly from one another and from Applicant's invention. While Eckenhoff is an implantable device for squeezing a substance out of a container, Biegajski is directed to water-soluble laminates that dissolve and which control the rates of delivery by way of different arrangements of different layers. Applicant's invention, in contrast, involves a particular wax-film composite including a pH-sensitive mucoadhesive and a water-insoluble wax layer bonded as a bi-layer film. The haphazard piecing together of elements of Eckenhoff and Biegajski reflected by the current rejections (1) still do not disclose, teach, or suggest the claims, (2) is impermissible because there is no motivation for the proposed combination of elements, and (3) lacks a reasonable expectation of success. The arguments presented to-date, therefore, have not established a *prima facie* case of obviousness.

Accordingly, Applicant respectfully asks the Board to favorably reconsider the patentability of the pending claims.

VIII. APPENDIX

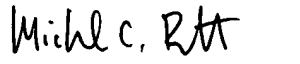
The pending claims are provided in the Claims Appendix.

IX. CONCLUSION

Applicant has provided arguments that overcome all the pending rejections. Applicant respectfully submits that the Office Action's conclusions that the claims should be rejected are unwarranted. It is therefore requested that the Board overturn the rejections.

Please date stamp and return the enclosed postcard to evidence receipt of this document.

Respectfully submitted,



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Date: June 20, 2005

CLAIMS APPENDIX

33. A wax-film composite comprised of a pH-sensitive mucoadhesive layer and a water-insoluble wax layer.

34. The wax-film composite of claim 33, wherein the pH-sensitive mucoadhesive layer is present at a concentration of 20% to 90% by weight, and the water-insoluble wax layer is present at a concentration of 10% to 80% by weight.

35. The wax-film composite of claim 33, wherein said pH-sensitive mucoadhesive layer is comprised of:

at least one water-insoluble swellable mucoadhesive polymer,

at least one pH-sensitive film-forming polymer, and

at least one molecule of interest.

36. The wax-film composite of claim 35, wherein the water-insoluble swellable mucoadhesive polymer is polyacrylic acid cross-linked with polyalkenyl ether or divinyl glycol.

37. The wax-film composite of claim 35, wherein the water-insoluble swellable mucoadhesive polymer is Noveon or Carbomer.

38. The wax-film composite of claim 35, wherein the water-insoluble swellable mucoadhesive polymer is present in the pH-sensitive mucoadhesive layer at a concentration from 0.1% to 20% by weight.

39 The wax-film composite of claim 35, wherein the pH-sensitive film-forming polymer present in the pH-sensitive mucoadhesive layer is a copolymer of methacrylic acid and acrylic or methacrylic ester.

40. The wax-film composite of claim 35, wherein the pH-sensitive film-forming polymer is present in the pH-sensitive mucoadhesive layer at a concentration from 0.05% to 10% by weight.

41. The wax-film composite of claim 35, wherein the pH-sensitive film-forming polymer present in the pH-sensitive mucoadhesive layer is a Eudragit polymer, or chemical derivative thereof.

42. The wax-film composite of claim 33, wherein the water-insoluble wax layer comprises at least one water-insoluble pharmaceutical wax having a melting point between 40° C and 100° C and at least one water-soluble or water-swellable polymer.

43. The water-insoluble pharmaceutical wax of claim 42, wherein said wax is DENTSPLY® Utility Wax, beeswax, emulsifying wax, microcrystalline wax, carnauba wax, paraffin wax, white wax, yellow wax, or other suitable pharmaceutical wax.

44. The water-soluble or swellable polymer of claim 42, wherein said polymer is present in the insoluble wax layer at a concentration from 0.05% to 10% by weight.

45. The water-soluble or swellable polymer of claim 42, wherein said water-soluble or water-swellable polymer is tragacanth, polyvinyl, pyrrolidone, polyvinyl alcohol, cross-linked polyacrylic acid, polyethylene glycol, a cellulose polymer derivative, or other suitable pharmaceutical polymer that is water-soluble or water-swellable.

46. The wax-film composite of claim 35, wherein the molecule of interest is contained in and released from either the pH-sensitive mucoadhesive layer or the water-insoluble wax layer.

47. The wax-film composite of claim 35, wherein the molecule of interest comprises an active pharmaceutical compound such as an antimicrobial, antiviral, antiinflammatory, antiseptic, antihistimine, a local anesthetic, a disinfectant, a keratolytic, an analgesic, an anti-migrane, anti-fungal, a sweetner, a flavoring agent, a diagnostic agent, or a combination thereof.

51. The wax-film composite of claim 35, wherein the molecule of interest is a peptide or protein.

56. The wax-film composite of claim 33, wherein the wax-film composite is applied to an application site comprising: the skin, mouth, vagina, nasal cavity, or other accessible mucosal site.

57. The wax-film composite of claim 56, wherein the wax-film composite adheres to the application site for at least one hour.

58. The wax-film composite of claim 33, wherein the wax-film composite has a total thickness of less than 5 mm.